

Automaticity and localisation of concurrents predicts colour area activity in grapheme-colour synaesthesia

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ABSTRACT

In grapheme-colour synaesthesia (GCS), the presentation of letters or numbers induces an additional 'concurrent' experience of colour. Early functional MRI (fMRI) investigations of GCS reported activation in colour-selective area V4 during the concurrent experience. However, others have failed to replicate this key finding. We reasoned that individual differences in synaesthetic phenomenology might explain this inconsistency in the literature. To test this hypothesis, we examined fMRI BOLD responses in a group of grapheme-colour synaesthetes ($n=20$) and matched controls ($n=20$) while characterising the individual phenomenology of the synaesthetes along dimensions of 'automaticity' and 'localisation'. We used an independent functional localiser to identify colour-selective areas in both groups. Activations in these areas were then assessed during achromatic synaesthesia-inducing, and non-inducing conditions; we also explored whole brain activations, where we sought to replicate the existing literature regarding synaesthesia effects. Controls showed no significant activations in the contrast of inducing > non-inducing synaesthetic stimuli, in colour-selective ROIs or at the whole brain level. In the synaesthete group, we correlated activation within colour-selective ROIs with individual differences in phenomenology using the Coloured Letters and Numbers (CLaN) questionnaire which measures, amongst other attributes, the subjective automaticity/attention in synaesthetic concurrents, and their spatial localisation. Supporting our hypothesis, we found significant correlations between individual measures of synaesthetic phenomenology and BOLD responses in colour-selective areas, when contrasting inducing against non-inducing stimuli. Specifically, left-hemisphere colour area responses were stronger for synaesthetes scoring high on phenomenological localisation and automaticity/attention, while right-hemisphere colour area responses showed a relationship with localisation only. In exploratory whole brain analyses, the BOLD response within several other areas was also correlated with these phenomenological factors, including the intra-parietal sulcus, insula, precentral and supplementary motor areas. Our findings reveal a network of regions underlying synaesthetic phenomenology and they help reconcile the diversity of previous results regarding colour-selective BOLD responses during synaesthesia, by establishing a bridge between neural responses and individual synaesthetic phenomenology.

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1. Introduction

Synaesthesia is a trait in which items of one perceptual class (inducers) consistently evoke additional 'concurrent' experiences in different perceptual categories. In grapheme-colour synaesthesia (GCS), letters or numbers (graphemes) trigger a concurrent

colour experience. Across fMRI studies of GCS, several areas have consistently shown increased activity when concurrents are reported, including left and right ventral-occipital areas (Laeng et al., 2011; Nunn et al., 2002; Rouw and Scholte, 2007; Steven, Hansen and Blakemore, 2006; Weiss et al., 2001) the superior and inferior parietal lobes (Laeng et al., 2011; Paulesu et al., 1995; Weiss et al., 2005), bilateral insula (Nunn et al., 2002; Paulesu et al., 1995; Sperling, Prvulovic et al., 2006) and the precentral gyrus (Laeng et al., 2011; Nunn et al., 2002; Paulesu et al., 1995; Rouw and Scholte, 2010; Weiss et al., 2005) (see Rouw et al., 2011, for a

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review). These activations have been proposed to support distinct roles in the generation of synaesthetic concurrences, such as binding of the synaesthetic colour and veridical letter (parietal), the affective response to concurrences (insular), interaction with the external environment and the cognitive control required in simultaneous processing of a synaesthetic and physical colour experience (precentral) (Rouw et al., 2011).

In contrast to these highly reliable findings, the activation of brain areas typically associated with veridical colour perception (e.g., human V4) has not been systematically replicated (e.g. Grey et al., 2006; Rich et al., 2006; Rouw and Scholte, 2007), leading Hupé and colleagues to conclude that “the neural bases of grapheme colour synaesthesia are not localised in real colour sensitive areas” (Hupé et al., 2012, p. 1622). In a review of synaesthesia fMRI investigations, Rouw et al. (2011) report that only five out of twelve studies identified V4 activation in response to synaesthetic colour: two in whole brain analysis, three in more statistically powerful region-of-interest (ROI) analyses. Where lateralisation information was additionally provided, the activation was bilateral in one investigation (Sperling et al., 2006), left hemisphere only in two investigations (Nunn et al., 2002; Steven et al., 2006), and right hemisphere only in one investigation. Methodological differences in task and analysis may account for some of this variation. For example, some studies used only small sample sizes (< 10 participants), thereby limiting their power. Additionally, not all investigations used retinotopic mapping to identify V4, and therefore conclusions drawn in these papers cannot be unambiguously linked to human V4. Having said this, colour-selective responses are not limited to V4, as shown by many functional localisation studies not related to synaesthesia (e.g. Howard et al., 1998). Indeed, in the original demarcation of V4 as a ‘colour sensitive area’, Zeki and Marini suggest that V4 is but one of the areas in a distributed network which supports colour processing (Zeki and Marini, 1998). With this in mind, it has been suggested that independent colour area localisation (e.g. contrasting coloured versus greyscale images) should be used to determine colour-specific regions in synaesthetes (Rouw et al., 2011).

Another important factor potentially underlying the variation in colour-selective responses observed during synaesthesia is variation in the synaesthetic experience itself. The simple idea is that synaesthetic experiences with ‘stronger’ colour phenomenology will more likely produce larger colour-selective responses. Phenomenological differences among (grapheme-colour) synaesthetes have typically been interpreted in terms of categorical projector-associator (PA) distinctions. This refers to the extent to which synaesthetes report their concurrences to be experienced with respect to an external reference frame (projector synaesthetes), or as an association with little or no externalised experience (associator synaesthetes).

Originally proposed by Dixon et al. (2004), the PA distinction has since been applied in a number of neuroimaging studies of GCS. Rouw and Scholte (2007) report a group difference in activation (synaesthetes > controls) in the right fusiform gyrus (FG) in the contrast of inducing > non-inducing graphemes. In their sample population, approximately 40% of synaesthetes were identified as projectors. Although structural brain properties were linked to individual differences in PA status in this study, there were no correlations between PA status and BOLD activity in the fusiform region (or indeed in any other region). In a subsequent study with a larger sample of synaesthetes ($n=42$), Rouw and Scholte (2010) did observe individual differences in BOLD activity related to PA status. Specifically, projectors showed less activity in inferior temporal regions (fusiform and parahippocampal gyrus) when experiencing synaesthetic concurrences, relative to associators and controls. Interestingly, no regions were found in which projectors showed more activity than associators. Independent

colour-area localizers were not used in these studies.

Projector-associator differences are also considered by Van Leeuwen et al. (2010), who did use an independent localizer to identify colour-specific ROIs within a region of the right FG, near V4, in a sample containing approximately 67% projectors. During synaesthetic experiences, they found a group difference in activation (synaesthetes > controls) in colour-specific ROIs, suggesting that this region is involved in both veridical and synaesthetic colour processing. However, a subsequent fMRI priming study in the same participants showed that synaesthetic colours do not prime subsequently presented real colours (based on repetition suppression effect in the BOLD signal) (Van Leeuwen et al., 2010). It was therefore concluded that synaesthetic colours and real colours both activate V4, but they do not share neural resources. In Van Leeuwen et al. (2010), neither the degree of V4 activity nor the degree of colour repetition suppression was related to PA status. In contrast, a separate study by the same authors did reveal a difference between projectors and associators during GCS, through Dynamic Causal Modelling (DCM) analysis. This fMRI analysis of effective connectivity suggested that projectors activated V4 via ventral stream inputs, while associators activated V4 via the parietal lobes (Van Leeuwen et al., 2011).

The above studies are dependent on the specific method used to characterise individual differences in the phenomenology of GCS. While the PA questionnaire has established construct validity (Anderson and Ward, 2015), it may miss important differences. For instance, some grapheme-colour synaesthetes don’t experience colours as projected onto the grapheme but experience them as appearing on a ‘mental screen’ (either externalised or internalized), while others merely claim to ‘know’ the colour (Ward, 2007). The latter two categories tend to be grouped as ‘associator’ though they clearly differ in terms of phenomenology (see also Van Leeuwen et al., 2010).

The Coloured Letters and Numbers (CLaN) questionnaire was developed by Rothen et al. (2013b) to give specificity to otherwise anecdotally reported individual differences in synaesthetic phenomenology, beyond those captured by the PA distinction. Data collection in an extended population of 628 grapheme-colour synaesthetes, together with a data-driven statistical analysis, identified four distinct factors in the phenomenological experience of GCS:

1. *Localisation*: The location of the synaesthetic experience, with higher scores denoting a tendency to experience concurrent colours at a specific location.
2. *Automaticity/Attention*: Higher scores indicate greater automaticity in synaesthetic concurrences, with less attention to the inducing stimulus needed for the synaesthetic experience to be elicited.
3. *Deliberate Use*: Higher scores indicate increased deliberate usage of synaesthetic experiences in everyday life, for example, in recalling telephone numbers.
4. *Longitudinal Changes*: Higher scores indicate that the intensity of synaesthetic colours has changed over time.

High localisation (CLaN-L) is similar but not identical to projector-like phenomenology. While both emphasize the importance of localisation, the PA scale but not CLaN, emphasizes the importance of ‘externalisation’. Rothen et al. (2013a) also note that questions addressing associator-like experiences (e.g. claims to “know” but not “see” synaesthetic colour), do not cluster with the CLaN-L questions in factor analysis, suggesting that associator-like phenomenology is independent from localiser phenomenology. The automaticity/attention factor (CLaN-AA) distinguishes synaesthetes on the degree to which concurrences are experienced automatically (i.e., with little attention afforded to the inducing

stimulus). Individuals with high CLaN-AA scores report experiencing concurrents readily whilst reading normal text, whilst those with low CLaN-AA scores report engaging in processes like active retrieval in order to experience concurrents. Synaesthesia is classically defined with reference to the 'automatic' nature of concurrents, however, the CLaN scale reveals that the degree of automaticity/attention is surprisingly variable across the population (Rothen et al., 2013b). CLaN-AA has also been shown to be negatively correlated to interference scores on a synaesthetic version of the Stroop task (Rothen et al., 2013b), which Hupé et al. (2012) reported to be negatively correlated (in non-parametric tests) with the BOLD response in visual areas.

In the present study we examine the impact of phenomenological variation in CLaN-L and CLaN-AA on the BOLD response to synaesthetic inducers in colour-selective areas. We used an independent functional colour-area localiser to identify colour-specific regions, so as to not be limited by retinotopic or anatomic demarcation of V4. Our primary hypothesis was that BOLD signal change in response to synaesthetic colour would correlate with individual phenomenological scores, both in regions sensitive to veridical colour and elsewhere in the brain.

This individual differences analysis provides improved power over a group analysis in a cohort of this size, and enables the detection of subtle effects. We hypothesised that CLaN-L would be positively correlated with BOLD response to synaesthetic colour in veridical colour-selective areas, as CLaN-L is conceptually related to projector-like phenomenology, and a significant response to synaesthetic colour within veridical colour-selective areas has previously been identified in sample populations with a high proportion of projectors (Rouw and Scholte, 2007; Van Leeuwen et al., 2010). We also hypothesised a positive correlation between BOLD response to synaesthetic colour in veridical colour selective areas and CLaN-AA, as CLaN-AA is inversely related to Stroop interference, which has been reported to be negatively correlated with the BOLD response in visual areas (Hupé et al., 2012). Since we had no specific hypotheses regarding the CLaN factors of Deliberate Use and Longitudinal Changes, these phenomenological factors were not included in our analyses. We also conducted exploratory analyses examining differences in left versus right hemisphere correlations with CLaN-L and CLaN-AA, and whole brain correlations with phenomenology, in order to investigate the wider impact of phenomenological variability on neuronal responses in grapheme-colour synaesthesia.

2. Methods

2.1. Participants

20 grapheme-colour synaesthetes (age 18–56 years, mean age 28.45 years; 13 female; 16 right handed) and 20 matched controls (age 19–52 years, mean age 28.5 years; 13 female; 16 right handed) were recruited via local advertising and from an existing pool of known grapheme-colour synaesthetes. Participants reported no history of neurological or psychological trauma and normal colour vision. Control participants reported no known synaesthesia of any form for themselves or first-degree relatives. GCS was confirmed in synaesthetic participants through completion of an online synaesthesia battery (Eagleman et al., 2007) and CIELUV transformed consistency scores in the range expected for GCS (Rothen et al., 2013a).

2.2. Synaesthesia phenomenology questionnaires

Synaesthesia phenomenology was assessed using the CLaN questionnaire (Rothen et al., 2013b). The CLaN questionnaire contains 30 items addressing localisation of synaesthetic colours, automaticity/attention in the synaesthetic experience, variability of the synaesthesia over time, and deliberate use of synaesthesia in everyday life. Questions were answered against a five point Likert scale of "strongly agree" to "strongly disagree". CLaN-L and CLaN-AA were assessed for multicollinearity and found to be uncorrelated ($r=.178$, $p=.226$) and statistically independent (Durbin-Watson $d=2.11$). Synaesthetes additionally completed the

Rouw and Scholte Projector-Associator Questionnaire (RS-PA) (Rouw and Scholte, 2007), to enable comparison of this cohort with those previously investigated.

2.3. Colour area localisation

Colour selective areas were functionally localised in each participant (synaesthete and control) using visual presentation of alternating blocks of coloured and greyscale Mondrian-style images, following the paradigm of Rich et al. (2006) (Fig. 1(A)). Stimuli were created and presented using Visual C# (Visual Studio 2010, Microsoft, Inc.). Coloured and greyscale stimuli were presented in six alternating blocks lasting 21 s each. Each block contained 14 stimuli, consisting of a foveal coloured or greyscale Mondrian presented against a grey background for 1000 ms, separated by a grey isoluminant screen for 500 ms. This gave a total of 84 stimuli per condition (coloured/greyscale) and a total run duration of 252 s.

2.4. Synaesthesia experiment

Stimuli used in the synaesthesia experiment included achromatic inducing letters (letters condition) and achromatic non-inducing punctuation symbols, e.g. &, %, # (symbols condition) (Fig. 1(B)). Stimuli were created and presented using Visual C# (Visual Studio 2010, Microsoft, Inc.). Inducing letters and non-inducing symbols were chosen on a participant-by-participant basis. Six inducing letters were selected for each synaesthete on the basis of their consistency in concurrent colour selection in the online Eagleman battery (Eagleman et al., 2007); the inducing letters condition contained only items for which the synaesthetes were able to identify their corresponding synaesthetic concurrent with a high degree of consistency, over repeated trials. Inducing letters were also selected to ensure a variety of synaesthetic colours which were distinct from the grey isoluminant background. For the non-inducing symbols condition, six common punctuation marks were individually identified as non-inducing by the synaesthete. Stimuli also included congruently and incongruently coloured inducers, and coloured non-inducers, as part of a separate study (see Gould et al., 2012).

Letters and symbols were presented foveally (2–6° of viewing angle) against a grey isoluminant background. Conditions were presented in a block design, with stimuli drawn randomly within each block from the set of six inducing letters or non-inducing symbols. Each run consisted of five blocks of each condition. Within each block, stimuli were presented for 2000 ms, separated with a 50 ms grey screen, with a total of 12 trials per block (block duration 24.6 s). Four runs were completed per participant, giving a total of 240 trials per condition per participant. Stimuli sets and block order for control participants were the same as those used for their matched synaesthete. Participants were instructed to silently name the letter or symbol for each presented item, in line with previous investigations of letter processing (e.g. Joseph et al., 2006, 2003).

2.5. Functional Imaging

MRI Data were acquired using a Siemens Avanto 1.5 T system. A T1 weighted structural image was acquired (TR 1160 ms, TE 44 ms, flip angle 15°, voxel size $0.9 \times 0.9 \times 0.9$ mm, 192 slices, 0.45 mm slice gap) followed by an echo-planar imaging sequence for functional volumes (TR 2210 ms, TE 30 ms, flip angle 90°, voxel size $3 \times 3 \times 3$ mm, 36 slices, 0.75 mm slice gap). The initiation of visual stimuli presentation was locked to the acquisition of the 6th volume, to allow for T1 saturation effects.

2.6. Image analysis

MRI data preprocessing and analysis was conducted using SPM8 (Wellcome Trust Centre for Neuroimaging, 2009), for both the colour area localiser and the synaesthesia experiments. Preprocessing consisted of slice timing correction, motion correction, normalisation to the SPM8 MNI T1 template, smoothing with an $8 \times 8 \times 8$ mm FWHM Gaussian kernel and high-pass filtering (128 Hz cut-off) to remove low-frequency effects. Condition blocks were modelled as a boxcar function convolved with the canonical haemodynamic response function. Realignment parameters were included as regressors of no interest in each first level model, to account for variance associated with participant motion. First level contrast images were then estimated in second level random effects and two-sample group designs, following the general linear model framework, to investigate group-by-condition interactions. In the synaesthesia experiment, the first eigenvariate of BOLD signal change was extracted from each cluster identified in the whole brain group-by-condition interaction, using a 5 mm ROI centred on the peak voxel of each cluster.

Colour-selective areas were defined separately for the left and right hemispheres in each participant, giving a total of two ROIs per participant. For each colour-selective area a single 8 mm radius ROI was centred on the peak response in each hemisphere in the first level contrast of coloured > greyscale Mondrians. The location of each individual peak response was limited by two inclusive masks. The first mask limited the search area to regions which were significant across both groups in second level parametric map (random effects analysis) of the contrast of

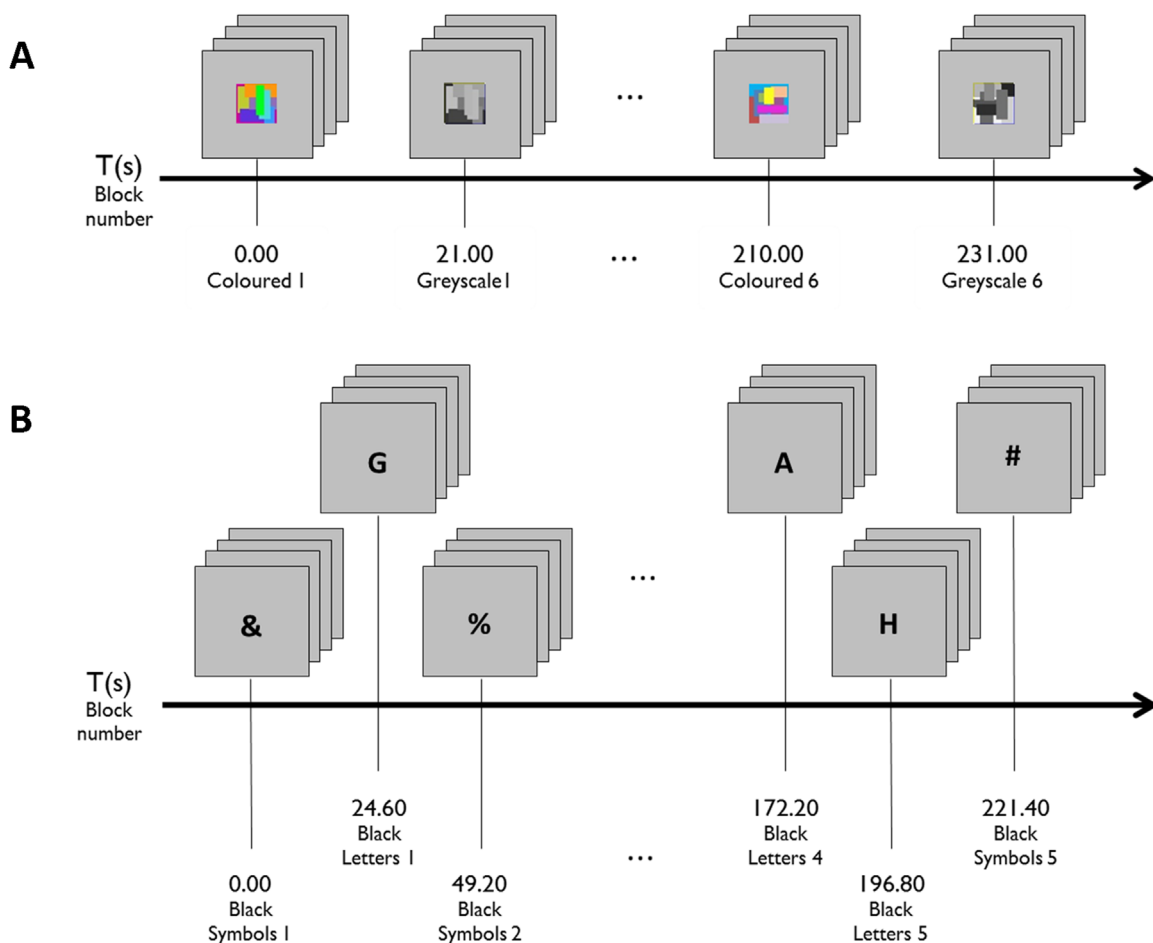


Fig. 1. Stimulus presentation structure fMRI experiments. A): A complete run of the colour area localiser, with six alternating blocks of coloured and greyscale Mondrian-like stimuli. B): A complete run of synaesthesia conditions, with achromatic inducing letters and achromatic non-inducing symbols. Synaesthesia stimuli sets were selected individually for each synaesthete, with the same set used for their matched control. (For interpretation of the references to colour in this figure, the reader is referred to the web version of this article.)

coloured Mondrians > greyscale Mondrians. This second level parametric map was thresholded at the liberal voxel level of height $p < .005$ and extent $k = 10$. From this map, a single large cluster survived cluster level FWE correction ($p < .05$), and spanned both hemispheres of the occipital lobe, including parts of V1, V2, V3, V4 and V5, as defined by the automated anatomical labelling atlas (Tzourio-Mazoyer et al., 2002). This cluster was converted into a binary inclusive mask, and applied to each first level map. Applying the random effects mask in this way ensured all individual colour-selective ROIs were within the area shown to consistently respond to colour across all participants. A second mask was then applied on top of the random effects mask, to limit the search area to the left hemisphere cortex, as defined by the automated anatomical labelling atlas (Tzourio-Mazoyer et al., 2002). The process was repeated for the right hemisphere ROIs: first level maps were overlaid with an inclusive mask of the combined group result of the colour localiser (contrast of coloured Mondrians > greyscale Mondrians) along with a right hemisphere cortex mask. For each hemisphere and each participant, the peak response was identified in the first level contrast of coloured Mondrians > greyscale Mondrians using a liberal uncorrected threshold of $p < .05$, $k = 10$, within the area defined by the two masks. This liberal threshold was necessary due to low statistical power in first level maps.

For two participants (one control and one synaesthete), a significant peak in the first level contrast of coloured Mondrians > greyscale Mondrians was identified in the left hemisphere at the uncorrected threshold of $p < .05$, $k = 10$, whilst activations in the right hemisphere were all $p > .05$ (uncorrected). In these cases, a right hemisphere ROI was created contralateral to the left hemisphere response by inverting the sign of the x co-ordinate. These, along with the individual defined areas, were used in all further ROI analyses (hence forth, referred to as “colour area ROIs”). Cluster analysis (k means) was conducted on the location of colour area ROIs from all participants collapsed together. The cluster analysis identified the centre of the colour area ROIs as the inferior occipital gyrus in the left hemisphere ($[-28, -72, -7]$) and the lingual gyrus in the right hemisphere ($[14, -85, -3]$).

In initial exploratory analyses, activation in the synaesthetes was regressed at the whole brain level against individual scores in the CLaN-L and CLaN-AA. Testing our specific hypotheses, hierarchical linear regression was conducted on the BOLD

response within colour-selective areas against CLaN-L and CLaN-AA. This enabled us to assess the influence of individual differences in synaesthesia phenomenology on colour area activity during synaesthesia conditions.

All whole brain second level statistical parametric maps were initially thresholded at the voxel level of $p < .005$ and extent of $k = 10$. Clusters were considered to be significant if they survived FWE correction for extent at the $p < .05$ level. Peaks were considered to be significant if they survived FWE correction for height at the $p < .05$ level.

3. Results

3.1. Phenomenology

The RS-PA questionnaire classified 2/20 participants as projectors (Fig. 2(A)). The CLaN factor of localisation (CLaN-L) is similar in kind to the RS-PA, and as expected, was significantly correlated with CLaN-L scores (Pearson's $r = .626$, $p = .002$, large effect) (Fig. 2(B)). In CLaN-L, however, three ‘associators’ (by RS-PA) scored equal to or higher in localisation than those identified as projectors (by RS-PA). This suggests that although there is general agreement between these two measures, they do not capture precisely the same phenomenological experience.

3.2. Colour area localiser

3.2.1. Whole brain

The pooled results from both synaesthetes and controls in the colour area localiser showed a significant FWE corrected peak in

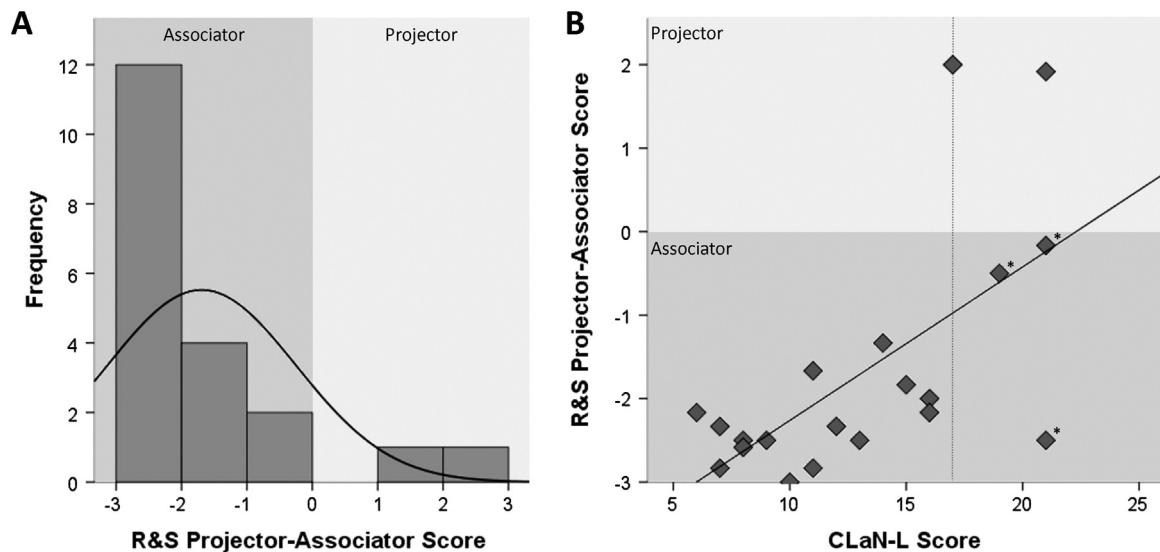


Fig. 2. Synaesthesia phenomenology scales. A) Classification of synaesthetes based on RS-PA measure qualifies two synaesthetes in the sample population as projectors. B) Correlation between RS-PA and CLaNL (Pearson's $r=.626$, $p=.002$, large effect). Dashed vertical line indicates lowest localisation score for a projector. Note that three associators (marked*) score higher in localisation than the lowest projector.

Table 1

Significant clusters and peaks in whole-brain analysis of coloured Mondrians > greyscale Mondrians. Areas identified from the combined data of all 40 participants. No significant FWE corrected whole-brain differences were identified between the groups. Areas labelled with the AAL toolbox for SPM (Tzourio-Mazoyer et al., 2002). Coordinates in MNI space.

Area	Cluster (p FWE)	Cluster k	Peak (p FWE)	Z	x	y	z
Fusiform gyrus (L)	< .001	6119	.002	5.525	-26	-68	-16
Calcarine sulcus (L)			.002	5.509	-12	-98	-2
Fusiform gyrus (L)			.004	5.398	-26	-78	-12

the left fusiform gyrus at $[-26, -68, -16]$ ($Z=5.52$, $p(\text{FWE peak})=.002$), close to previously reported co-ordinates for V4. Further significant peaks were also identified in the left calcarine sulcus at $[-12, -98, -2]$ ($Z=5.51$, $p(\text{FWE peak})=.002$) and the left fusiform gyrus at $[-26, -78, -12]$ ($Z=5.40$, $p(\text{FWE peak})=.004$) (see Table 1). These findings are in agreement with previous investigations of colour selective areas (Rouw et al., 2011), indicating that we successfully localised colour selective responses in these participants. No significant group differences were found between synaesthetes and controls in response to the colour area localiser.

3.2.2. Colour area ROI analysis

Colour area ROIs were generated separately in the left and right hemisphere for each synaesthete and control. ROIs were located at the region of the peak response in first level analysis of the contrast coloured Mondrians > greyscale Mondrians, and within the area of significant activation across all participants collapsed together (Fig. 3).

To assess potential differences in colour-specific responses between synaesthetes and controls across the left and right hemisphere colour-selective ROIs, we conducted a mixed ANOVA with the between-subjects factor 'group' (synaesthetes and controls) and the within-subjects factor 'ROI hemisphere' (left, right). There was significant main effect of group ($F(1,38)=4.245$; $p=.046$), with increased activation in synaesthetes ($\text{mean}=0.495$; 95%CI = 0.411–0.579) compared to controls ($\text{mean}=0.374$; 95%CI

= 0.290–0.458). There was no significant main effect of ROI hemisphere ($F(1,38)=.294$, $p<.591$) demonstrating that there is no significant difference in activation between the left and right colour-selective areas. There was no significant ROI hemisphere-by-group interaction ($F(1,38)=.607$; $p=.441$), indicating that there was no significant difference between activation in left and right hemisphere ROIs dependent on group membership.

3.3. Synaesthesia experiment

3.3.1. Whole brain

In synaesthetic colour processing, there was a group-by-condition interaction (synaesthetes [letters > symbols] > Controls [letters > symbols]), with significant FWE corrected clusters of activation ($p(\text{FWE cluster})<.05$) in the left precentral gyrus and bilateral inferior parietal gyrus (Fig. 4). Derived BOLD signal changes showed interactions were driven by group differences in letter processing in the left precentral and left inferior parietal clusters, and by symbol processing in the right inferior parietal cluster (see Fig. S2).

The pattern of activation is consistent with those areas identified by the Rouw et al. (2011) review as being highly reproducible across different investigations of GCS. (Fig. S1 superimposes our results on the regions identified in the meta-analysis of Rouw et al., 2011). Strikingly, there were no significant peaks or clusters in the region of V4 when assessing whole-brain group differences in the group-by-condition interaction.

3.3.2. Colour area ROI analysis

Activation in colour area ROIs, was assessed under synaesthetic conditions. As described in Section 2.6, colour area ROIs were centred on the peak response in each first level analysis of coloured Mondrians > greyscale Mondrians, within the area identified as significant in the second level analysis of the same contrast.

There was no significant main effect of group in the group-by-ROI mixed ANOVA for the contrast of inducing letters > non-inducing symbols ($F(1, 38)=3.047$, $p=.089$), and no significant group-by-ROI interaction ($F(1, 38)=0.013$, $p=.912$). This suggests that at the group level, there is no significant difference in colour area activation between synaesthetes and controls in response to synaesthetic colour, even in sensitive ROI level analyses. This is in

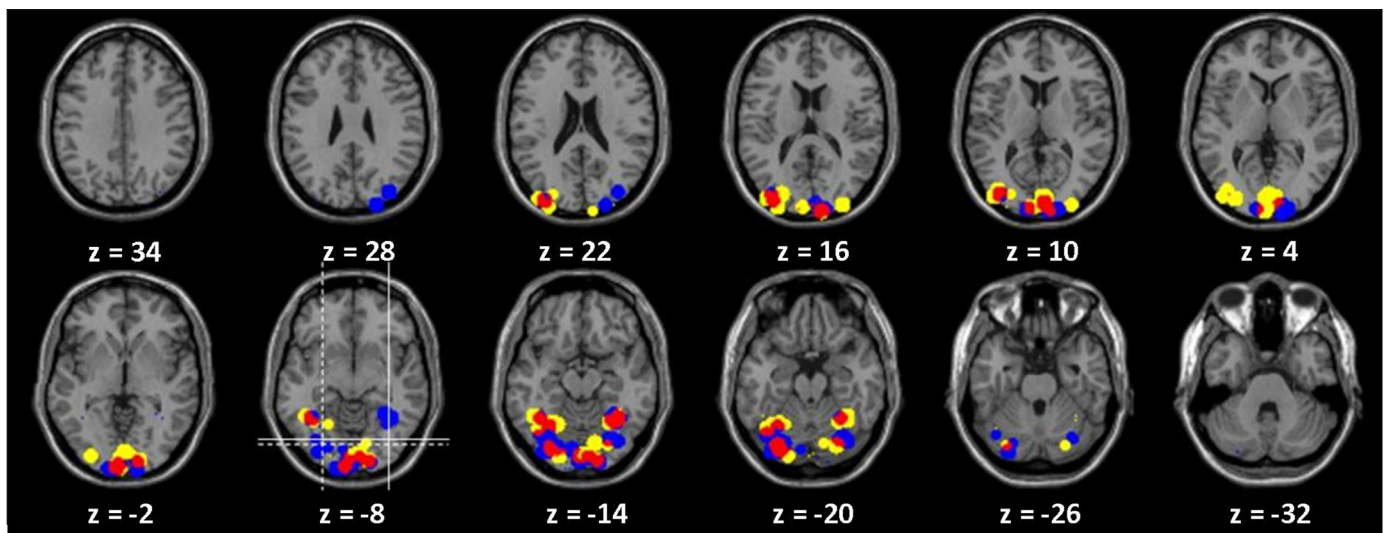


Fig. 3. Positioning of participant colour-selective 8 mm radius ROIs in axial slices from $z = 34$ to $z = -32$. Peak colour-selective responses show a similar distribution in both synaesthetes (blue) and controls (yellow). Overlapping areas shown in red. Approximate location of V4 indicated with white crosshairs (left $[-29, -76, -7]$; right $[33, -72, -10]$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

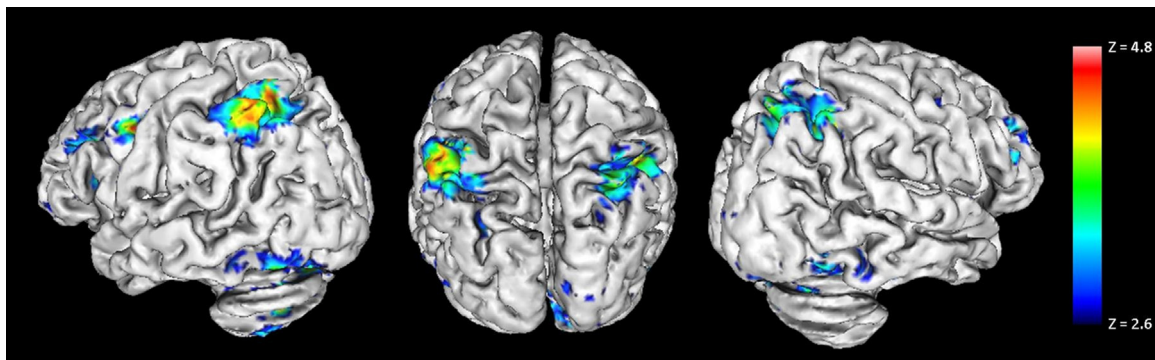


Fig. 4. Two sample t -test (synaesthetes > controls) on main effect of condition (letters > symbols). Significant FWE corrected clusters in: left precentral cortex $[-46, 4, 34]$ ($k = 437$, $p(\text{FWE cluster}) = .023$, $Z = 4.051$, $p(\text{FWE peak}) = .603$); left inferior parietal cortex $[-46, -48, 50]$ ($k = 750$, $p(\text{FWE cluster}) = .001$, $Z = 4.050$, $p(\text{FWE peak}) = .604$); right inferior parietal cortex $[44, -48, 48]$ ($k = 480$, $p(\text{FWE cluster}) = .014$, $Z = 3.765$, $p(\text{FWE peak}) = .902$). Data demonstrate that group-by-stimulus effects are consistent with Rouw et al. (2011) (see also Fig. S1). Colour scale represents Z-score range from 2.6 to 4.8, equivalent to uncorrected height threshold $p < .005$ to $p < .001$.

accordance with the majority of the existing literature in which colour area activation in response to synaesthetic inducers has not reliably been found (Rouw et al., 2011).

3.4. Individual differences

3.4.1. Whole brain

We performed whole-brain regression analysis on the contrast letters > symbols in synaesthetes (not controls), against the factor scores for CLaN-L and CLaN-AA. Significant positive relationships were found between BOLD signal and CLaN scores in several distinct areas (see Table 2 and Fig. S3). Synaesthetes with more localised concurrents (measured by CLaN-L) showed greater activation in the left precentral gyrus, left insula, right cerebellum, left anterior intra-parietal sulcus and left supplementary motor area. The cluster in the left precentral gyrus shows considerable overlap with the left precentral cluster identified in between-group contrast (Section 3.3.1), suggesting that this area is relevant to synaesthetic colour processing and is also related to the phenomenological variation within this cohort (all other whole-brain regression clusters are distinct from the group interactions). With respect to automaticity/attention, a cluster of activation in the right middle occipital gyrus showed a significant positive relationship with CLaN-AA. This analysis of whole brain individual

Table 2

FWE corrected clusters of BOLD activation identified in whole-brain regression analysis of synaesthetes in the contrast letters > symbols. Areas labelled with the AAL toolbox for SPM (Tzourio-Mazoyer et al., 2002). Coordinates in MNI space. See also Fig. S2.

Area	Cluster (p FWE)	Cluster K	Peak (p FWE)	Z	x	y	z
Synaesthetes: CLaN-L							
Precentral (L)	<.001	743	.802	4.006	-44	2	36
Insula (L)	.038	341	.894	3.899	-34	16	10
Cerebellar Crus1 (R)	.013	421	.955	3.790	38	-70	-32
Anterior intra-parietal sulcus (L)	.042	334	.964	3.768	-20	-36	30
Supplementary motor area (L)	.006	489	.988	3.668	-8	4	62
Synaesthetes: CLaN-AA							
Middle occipital (R)	.001	661	.642	4.140	40	-74	2

differences suggests that localisation and automaticity/attention in concurrents correlates with activation in key synaesthesia-related areas (left precentral gyrus), as well as in insular, intra-parietal, motor and occipital areas.

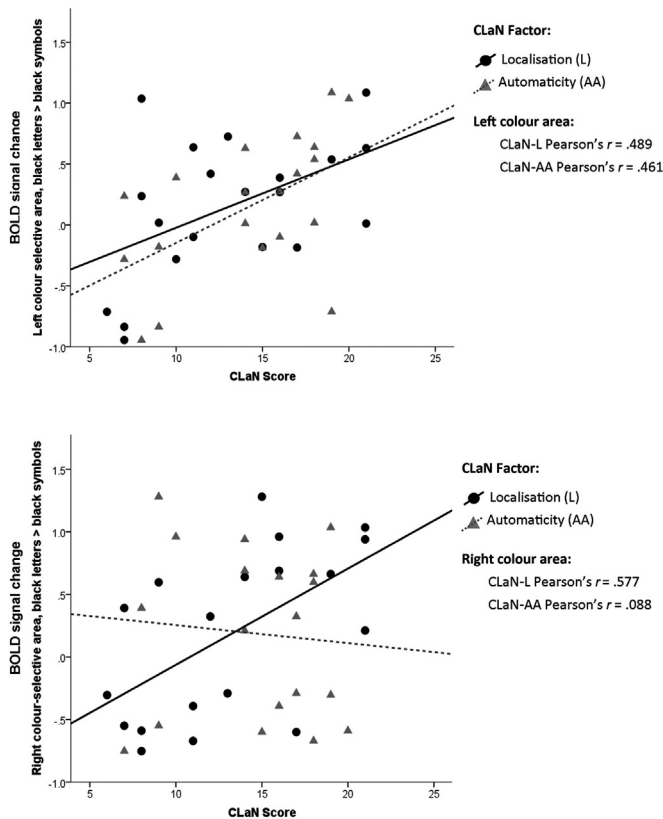


Fig. 5. Linear regressions of colour-selective ROI responses (BOLD signal change) in left (top, $n=20$) and right hemispheres of synaesthetes (bottom, $n=19$), during the main effect of synaesthesia (letters > symbols). Regression against CLaN-L (black circles) and CLaN-AA (grey triangles). Note one participant was removed from right hemisphere ROI analysis as an outlier. See Table S1 for ROI locations.

3.4.2. Colour-area ROI analysis

In assessment of our primary hypothesis, individual differences in activation within colour area ROIs were assessed under synaesthetic conditions. Colour area ROIs were located as described in Section 2.6.

Confirming our primary hypothesis, we found a significant positive relationship between localisation scores (measured by CLaN-L) and the BOLD response to synaesthetic colour in left hemisphere colour area ROIs (Pearson's $r = .489$, $p = .029$, medium effect) and in the right hemisphere (Pearson's $r = .577$, $p = .010$, large effect). In addition, there was a significant positive relationship between automaticity (CLaN-AA) and the BOLD response to synaesthetic colour in left hemisphere colour area ROIs (Pearson's $r = .461$, $p = .022$, medium effect), but not right hemisphere colour area ROIs (Pearson's $r = .088$, $p = .363$, no effect) (Fig. 5).

Hierarchical regression models were constructed with the inclusion of both CLaN-L and CLaN-AA to determine the relative contribution of each variable in estimating the degree of colour area response during synaesthesia. The top level of the hierarchical models was assigned to CLaN-L as this measure best captured our starting hypothesis of a relationship between the projector-type phenomenology and colour area activation. There was no evidence of multicollinearity; bivariate correlations between ROI activation for CLaN-L and CLaN-AA r range = .178–.534; tolerance $T = 0.968$; variance inflation factor = 1.033. There was slight negative autocorrelation (Durbin-Watson $d = 2.331$) but this is within the acceptable limits of 1.5–2.5. This suggests that the colour area activations and CLaN measures are statistically independent from each other.

Table 3

Hierarchical regression models of BOLD signal change in synaesthetes' colour selective areas in the contrast letters > symbols against CLaN-L and CLaN-AA.

Predictor variable	beta	SE (beta)	β	R^2 Adj.	F	p (F)	p (ΔF)
<i>Left colour selective area – Model 1</i>							
CLaN-L	.056	.024	.489 ⁺	.197	5.670 [†]	.029 ⁺	
<i>Left colour selective area – Model 2</i>							
CLaN-L	.047	.021	.407 ⁺	.380	6.833 [‡]	.007 ^{***}	.022 ⁺
CLaN-AA	.061	.024	.461 ⁺				
<i>Right colour selective area – Model 1</i>							
CLaN-L	.077	.026	.577 ⁺	.294	8.500 [§]	.010 ⁺	
<i>Right colour selective area – Model 2</i>							
CLaN-L	.080	.027	.600 ^{***}	.281	4.517	.028	.419
CLaN-AA	−0.027	.033	−.167				

⁺ $p < .05$.

^{***} $p < .01$.

[†] Degrees of freedom = 1,18 ($n=20$).

[‡] Degrees of freedom = 2,17 ($n=20$).

[§] Degrees of freedom = 1,17 ($n=19$).

^{||} Degrees of freedom = 2,16 ($n=19$).

Based on the regression analysis, the data in the left hemisphere are best fit by a model which includes both CLaN-L and CLaN-AA scores (Table 3, left colour selective area - Model 2), as compared to a model which includes only CLaN-L (Table 3, left colour selective area - Model 1), or the mean activation (both Model 1 and 2 are significant). In right hemisphere colour selective areas, the data are best fit when modelled using CLaN-L alone (Table 3, right colour selective area - Model 1). This suggests that both localisation and automaticity/attention predict the degree of colour-area activation in response to the synaesthetic colour experience, i.e. estimating the BOLD signal change in response to synaesthetic colour, within in colour selective ROIs, is helped by knowing the degree of phenomenological localisation and automaticity in synaesthetic concurrents.

In exploring lateralisation effects, CLaN-L correlates with the activation in both left and right hemisphere colour areas, whereas CLaN-AA only provides significant improvement in the model for responses in the left hemisphere. Interestingly, the standardised β for CLaN-AA in the left hemisphere is greater than that for CLaN-L in the left hemisphere, suggesting CLaN-AA has a greater predictive power for colour area activation in the left hemisphere, than CLaN-L.

In summary, we found that BOLD responses to synaesthetic inducing stimuli are associated with individual differences in CLaN-L and CLaN-AA phenomenology, across precentral, insular, intra-parietal, occipital and motor areas. We also found that specific colour area activation is predicted by both CLaN-L and CLaN-AA in the left hemisphere, and by CLaN-L alone in the right hemisphere.

4. Discussion

We examined the impact of individual differences in synaesthetic phenomenology, as measured by CLaN-L and CLaN-AA, on BOLD responses to synaesthetic colour in colour selective areas, and across the whole brain. Using a functional colour-area localiser, we successfully identified 'colour-selective' regions in the fusiform gyrus, with a peak close to reported locations of V4 (Table 1). This activation map was then used to define individual colour-selective areas for synaesthetes and controls. The maximal colour-selective responses for each participant showed variation in their anatomical location, as reported elsewhere (e.g. Mckeefry and Zeki, 1997), but a large proportion were localised to the lateral bank of the contralateral sulcus in both synaesthetes and controls

(Fig. 3). In synaesthetic colour processing (inducing letters > non-inducing symbols), there was a significant group interaction (synaesthetes > controls) in the left precentral gyrus and bilateral inferior parietal gyrus (Fig. 4) in line with previous reports (Rouw et al., 2011), but there was no evidence of significant activation in the region of V4. At the group level, there was no significant group interaction in the BOLD response to synaesthetic colour within colour-selective ROIs. Crucially, individual differences in the phenomenological measures CLaN-L and CLaN-AA predicted BOLD responses in individually-defined colour-selective areas. This finding supports our primary hypotheses that activation within veridical colour areas in response to synaesthetic colour depends on individual (synaesthetic) phenomenology. In addition, exploratory analysis of whole brain correlations with CLaN-L and CLaN-AA indicate that activation in the left precentral gyrus, insular, intra-parietal sulcus, supplementary motor and middle occipital areas, under synaesthetic conditions, is also associated with phenomenological variability in these factors.

These data demonstrate that individual differences in synaesthetic phenomenology significantly impact the degree of BOLD response to synaesthetic colour processing, across multiple brain areas and including colour-selective regions. This finding may help resolve the conflict in the synaesthesia literature regarding the replication of key findings implicating colour-selective responses to inducing stimuli, and issues of low power (Hupé and Dojat, 2015). Specifically, we found that the greater the (phenomenological) localisation of the synaesthetic concurrent, the greater the activation in both left and right hemisphere colour-selective areas. This suggests that previous conflicting reports of colour area activation may be confounded by the choice of participants rather than (or in addition to) methodological differences. Our data also speak to conflicting reports in lateralisation in colour area responses. For example, Nunn et al. (2002) reported left hemisphere V4 activation in synaesthetic conditions, whereas both Rouw and Scholte (2007) and Van Leeuwen et al., (2010) reported right hemisphere V4 activation. Our investigation of individual differences suggests that inconsistencies in lateralisation may be due to phenomenological variation in participants, with localisation correlating with the degree of colour-area activation in both left and right hemispheres, and automaticity/attention correlating with colour-area activation in the left hemisphere only.

In a recent review of the GCS imaging literature, Hupé and Dojat (2015) report that of the 25 studies considered, only five were compatible with the involvement of colour regions in grapheme-colour synaesthesia. Hupé and Dojat (2015) cite problematic interpretations of control conditions and low statistical power for the lack of supporting evidence for colour-area involvement. They suggest that the individual differences in synaesthetic phenomenology do not account for failed replications, on the grounds that no correlations were observed between V4 activity and performance in a visual search task (Hubbard et al., 2005), whilst a negative correlation was observed between “photism strength” (calculated from Stroop interference in synaesthetic colour naming) and BOLD response in V4 (Hupé et al., 2012).

Contrary to Hupé et al. (2012), we demonstrate a positive correlation between left hemisphere colour-area activity and CLaN-AA. We suggest that the disparity between the results presented here and the conclusions of Hupé et al. (2012) may be due to the inverse correlation between Stroop interference and CLaN-AA, as demonstrated by Rothen et al., (2013b). Since CLaN-AA and Stroop interference are negatively correlated, it follows that the positive correlation between CLaN-AA and BOLD identified here may be manifest as a negative correlation between Stroop interference (as a function of “photism strength”) and BOLD in Hupé et al. (2012). Thus the present findings are consistent with those of Hupé et al. (2012) when accounting for failure to find colour-selective activity

in synaesthesia, and if sample populations contain a high degree of participants who score low on CLaN-AA and conversely, high on Stroop interference.

A positive relationship between CLaN-L and colour-specific activation is consistent with previous studies where the projector-associator measure has been utilised. Specifically, a BOLD response in the fusiform gyrus (near V4) has previously been identified in sample populations containing a high proportion of projectors. For example, Rouw and Scholte (2007) report a group interaction (synaesthetes > controls) in synaesthetic colour processing, with increased activation in the right fusiform gyrus during synaesthetic colour processing in synaesthetes compared to controls. Approximately 40% of the synaesthetes in the sample of Rouw and Scholte (2007) were classified as projectors. Van Leeuwen et al., (2010) also report right fusiform gyrus activation to synaesthetic colour, in a sample which comprised of between 37 and 74% projectors, depending on how their ‘mental screen projectors’ are classified. Although high localisation and projector-like phenomenology are not equivalent, they are conceptually and statistically related (Fig. 2(B)). The localisation of a concurrent according to the CLaN-L measure refers to the degree to which a synaesthete reports to experience colours in a specific location. That location need not be externalised (cf. ‘projectors’, who report to see a concurrent in external space), but those scoring high on CLaN-L do report their concurrent to be more ‘percept-like’. For instance, the statement “I do not ‘see’ colours when I look at the letters/numbers” loads negatively on to his factor whereas the statement “I can point to the location of the synaesthetic colours” loads positively. Thus the ‘percept-like’ nature of high localisation and projector-type phenomenology, supports the identification of a colour-area response in sample populations comprised of a high proportion of either high localisers or projectors.

Beyond colour-selective responses, our whole brain analysis identified a number of areas in which activation to synaesthetic colour was correlated with individual differences in synaesthetic phenomenology. Within visual cortex, CLaN-AA correlated with activation in a region of the right middle occipital gyrus; probabilistic histological labelling (Eickhoff et al., 2005) suggests the majority of this cluster is located in V4 and V5, however, the peak is more lateral and ventral than areas normally implicated in colour processing (e.g. Zeki and Marini, 1998), or the colour selective areas identified here. This suggests that whole brain analysis is not sufficiently sensitive to detect the relationship between CLaN-AA and colour-area response. Outside visual areas, the activation of motor-related regions (including precentral gyrus) is commonly found in synaesthetic colour processing (Rouw et al., 2011) but has remained largely unexplained. One suggestion is that activation in these areas relates to “sensing of and acting on the outside world” (Rouw et al., 2011, p. 227). Our finding of a positive correlation between CLaN-L and primary motor (precentral) and supplementary-motor area activation supports this suggestion, inasmuch as a localised concurrent promotes a stronger motor response, even when no motor task was employed. Notably, CLaN-L has items relating to “I can point to the location of the synaesthetic colour”, and similarly, “I can choose to alter the location of the synaesthetic colours”, both of which suggest action.

A potential limitation in this investigation relates to the unexplored relationships between CLaN-L, CLaN-AA and mental imagery, with the possibility that mental imagery may be a common and confounding factor driving the relationship between CLaN-L/CLaN-AA and colour-area activation. It is not known whether CLaN-L and CLaN-AA relate to mental imagery, however it has been noted that synaesthetes typically show increased mental imagery (Barnett and Newell, 2008; Janik McErlean and Banissy, 2016; Spiller et al., 2015) and a more visual cognitive style compared to controls (Meier and Rothen, 2013). It has also been

demonstrated that voluntary colour imagery may be associated with colour-area activation in both synaesthetes and controls (Rich et al., 2006). These findings have been proposed to explain differences in colour-area activation between synaesthetes and controls (see for example Chiou and Rich, 2014), however they have not been related to variations in colour area activation *within* a synaesthetic population, as in the present investigation. If CLaN-L and CLaN-AA are related to imagery, the correlation between CLaN-L/CLaN-AA and colour area-activation reported here may simply reflect the known relationship between *imagery* and colour-area activation.

Although Imagery Ability is increased in GCS (Mealor et al., submitted), unpublished data ($n=30$ GCS) suggest Imagery Ability is not correlated with CLaN-L (Pearson's $r=.085$, $p=.645$) nor CLaN-AA (Pearson's $r=.212$, $p=.260$). The Imagery Ability factor of the Sussex Cognitive Styles Questionnaire (SCSQ) (Mealor et al., submitted) includes questions related primarily to object imagery, based on the Object Spatial Imagery and Verbal Questionnaire (OSIVQ) (Blazhenkova and Kozhevnikov, 2009) and the 'Habitual Use of Imagery' subscale of the Individual Differences Questionnaire (Paivio and Harshman, 1983; Paivio, 1971). These items relate to the tendency or ability to form vivid visual images of objects, which is distinct from spatial aspects of imagery (a separate factor in both in the OSIVQ and the SCSQ). These data suggest the relationship between colour area activation and synaesthetic phenomenology reported here is not due to variations in mental imagery abilities, however further investigation will be required in order to determine whether this observation holds for larger sample sizes.

In summary, our results address a long-standing conflict in the synaesthesia literature regarding fMRI BOLD responses in colour-specific areas during grapheme colour synaesthesia (GCS). Adopting a neurophenomenological approach, we correlated precise descriptors of the phenomenological experience of GCS with BOLD responses in a large sample of synaesthetes, finding that colour-specific activity in response to inducers has a positive relationship with CLaN-L and CLaN-AA in the left hemisphere, and with CLaN-L in the right hemisphere. Importantly, colour-specific regions were identified for each participant using independent functional localizers. Together, our data suggest that conflicting results regarding activation of real colour selective areas during synaesthetic conditions can be attributed to individual differences in phenomenology, specifically the independent factors of localisation and automaticity/attention in concurrents. Our investigation supports the identification of a neural basis of synaesthetic colour in colour-selective areas, and in doing so provides an instructive example of the value of considering precise phenomenological descriptors when assessing the neural basis of conscious experience.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.neuropsychologia.2016.04.016>.

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